IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0282/026/002
Case No: 2061908

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Norton Healthcare Limited T/A IVAX Pharmaceuticals UK

Regent House, 5-7 Broadhurst Gardens, **Swiss Cottage**, **London NW6 3RZ**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Metronidazole Tablets BP 400mg.

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/06/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metronidazole Tablets BP 400mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of metronidazole.

Excipient: Lactose monohydrate 150mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, circular, biconvex tablets having a diameter of 12.5 mm. Coded 'MZL 400' with breakline on one face, twin triangle logo on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the treatment of urogenital trichomoniasis.
In the treatment of acute ulcerative gingivitis.
In the treatment of infections due to *E. histolytica* (including carrier states).
In the treatment of infections due to *G. lamblia* (including carrier states).
In the prevention and treatment of infections due to anaerobic bacteria, particularly species of *Bacteroides, anaerobic streptococci, fusobacteria, clostridia*, etc.
In the treatment of acute dental infections.
In the treatment of chronic pressure sores and ulcers with possible infection due to anaerobes.
In the treatment of non-specific vaginitis.

4.2 Posology and method of administration

1) <u>Urogenital trichomoniasis</u>

<u>Adults and Children over 10 years:</u>
600 mg daily in divided doses for 7 days. (Where appropriate the partner should be treated at the same time).

A short two day course of 2 g in two divided doses daily may be used, or a single dose of 2 g.

<u>Children:</u>

Aged 7-10 years	300 mg daily in three divided doses.
Aged 3-7 years	200 mg daily in two divided doses.
Aged 1-3 years	150 mg daily in three divided doses.

Treatment to continue for 7 days.

2) Acute ulcerative gingivitis

Adults and Children over 10 years:
600 mg daily in divided doses for 3 days.

Children:

Aged 7-10 years	300 mg daily in three divided doses for 3 days.
Aged 3-7 years	200 mg daily in two divided doses for 3 days.
Aged 1-3 years	150 mg daily in three divided doses for 3 days.

3) Amoebiasis

Adults and Children over 10 years:
1200-2400 mg daily in three divided doses.

Children

Aged 7-10 years	600-1200 mg daily in three divided doses.
Aged 3-7 years	400-800 mg daily in four divided doses.
Aged 1-3 years	300-600 mg daily in three divided doses.

Treatment is usually required for 5 to 10 days.

4) Giardiasis

Adults and Children over 10 years:
2000 mg once daily for 3 days.

Children

Aged 7-10 years	1000 mg once daily for 3 days.
Aged 3-7 years	600 mg once daily for 3 days.
Aged 1-3 years	400-500 mg once daily for 3 days.

5) Anaerobic Infections

Treatment

Adults:
800 mg followed by 400 mg 8 hourly.

Children:
7.5mg/kg 8 hourly.

Treatment should be continued as indicated by the clinical and bacteriological assessment by the clinician, but seven days should generally be sufficient.

Prophylaxis against Anaerobic infections

Adults:
400 mg at 8 hourly intervals during the 24 hours immediately preceding operation, followed post operatively by intravenous or rectal administration until oral dosing can be resumed.

Children:
7.5mg/kg 8 hourly.

6) Dental Infections

The usual total daily dosage is 600 to 800 mg in divided doses.
Treatment should generally be continued for 3-7 days.

7) Chronic pressure sores and ulcers

Adults:
1200 mg daily in three divided doses.

8) Non-specific Vaginitis

Adults and children over 10 years:
A single dose of 2 g may be used or 400 mg twice daily for 7 days.

Adjustment of dosage does not appear necessary in patients with renal impairment.

In the case of children whose weights are below those usual for their age, or of infants below 10kg in weight, dosage of metronidazole should be reduced proportionately.

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Hepatic Encephalopathy
Daily dosage should be reduced to one third and may be given once daily (*see section 4.4, Special warnings and precautions for use*).

Elderly:
Caution is advised, particularly at high doses. No information is available on modification of dosage.

Route of Administration

Oral.

4.3 Contraindications

Use in patients with known hypersensitivity to metronidazole, nitroimidazole derivatives or to any of the excipients.

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.

4.4 Special warnings and precautions for use

If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. It is recommended that haematological tests be carried out regularly and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures). The appearance of abnormal neurological signs demands the prompt discontinuation of metronidazole.

High dosage regimes have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Patients with rare hereditary problems of galactose intolerance, the Lapp Lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Metronidazole has been shown to be carcinogenic in the mouse and rat. However, similar studies in the hamster have given negative results and extensive human epidemiological studies have provided no evidence of increased

carcinogenic risk in humans. Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro as well as in rodents and in humans in vivo, there was inadequate evidence of a mutagenic effect of metronidazole. Therefore the use of metronidazole for longer treatment than usual should be carefully weighed.

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The daily dosage should be reduced to one third. The risk/benefit using metronidazole to treat trichomoniasis in such patients should be carefully considered.

Metronidazole should be administered with caution to patients with hepatic encephalopathy.

Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite)

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards (*see section 4.5 Interaction with other medicinal products and other forms of interaction*).

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidal agent.

Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.

There is a possibility that after Trichomoniasis vaginalis has been eliminated a gonococcal infection might persist

4.5 Interaction with other medicinal products and other forms of interaction

Potentiation of the anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic catabolism. In case of coadministration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole.

Lithium retention observed by increased plasma lithium levels, accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Plasma levels of lithium may be increased by metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Phenytoin or Phenobarbital: increased elimination of metronidazole resulting in reduced plasma levels. A similar effect may occur with other drugs which induces hepatic microsomal enzymes

Patients should be advised not to take alcohol, (or drugs containing alcohol) during metronidazole therapy and for at least 48 hours afterwards because of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).

Disulfiram: psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Cyclosporin: risk of elevation of the cyclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

5 Fluorouracil: reduced clearance of 5 fluorouracil resulting in increased toxicity of 5 fluorouracil.

Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

Cimetidine: The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

Metronidazole may interfere with certain types of determinations of serum chemistry values such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides and glucose hexokinase

4.6 Pregnancy and lactation

Metronidazole should only be used during pregnancy or lactation following careful evaluation and only if considered essential by the physician. Its effects on foetal organogenesis are not known. If used, high dosage regimes should be avoided. The drug crosses the placenta and is excreted in breast milk in which concentrations equal those in serum. Unnecessary exposure to the drug should be avoided.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for confusion, dizziness, hallucinations or convulsions, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

Gastrointestinal effects
- epigastric pain, nausea, vomiting, malaise, diarrhoea
- oral mucositis, taste disorders, dry mouth, anorexia, coated tongue
- exceptional and reversible cases of pancreatitis.

Hypersensitivity reactions
- rash, pruritus, flushing, urticaria, erythema multiforme
- fever, angioedema, exceptional anaphylactic shocks
- very rare pustular eruptions.

Peripheral and central nervous system
- peripheral sensory neuropathy, paraesthesia
- headache, convulsions, dizziness, in-coordination, syncope, taste metallic
- very rare reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor) which may resolve with discontinuation of the drug.

Psychiatric disorders
- psychotic disorders including confusion, hallucinations
- depressed mood

Vision disorders
- transient vision disorders such as diplopia, myopia.

Haematology
- leucopenia and very rare cases of agranulocytosis, neutropenia, and thrombocytopenia have been reported.

Liver
- very rare cases of reversible abnormal liver function tests and cholestatic hepatitis sometimes with jaundice have been reported.

Musculoskeletal, connective tissue and bone disorders
- arthralgia and myalgia

Renal and urinary disorders
- brown urine

4.9 Overdose

Treatment of overdosage:

Single oral doses of metronidazole, up to 12 g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. There is no specific treatment for gross overdosage of metronidazole. In cases of suspected massive overdose, symptomatic and supportive treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antiprotozoals, Nitroimidazole derivative P01A B

The drug has antiprotozoal and antibacterial actions including activity against anaerobic bacteria, *Entamoeba histolytica*, etc.

5.2 Pharmacokinetic properties

A nitroimidazole derivative well absorbed and widely distributed in the body. It is metabolised by hepatic acid oxidation, hydroxylation and glucuronidation and excreted in urine and faeces with a T½ of about 6-10 hours. Metronidazole is excreted in milk but the intake of a sucking infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

5.3 Preclinical safety data

None

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize Starch
Povidone
Magnesium Stearate
Colloidal Anhydrous Silicia

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special precautions for storage

Do not store above 25^0 C. Protect from light. Store in the original Package.

6.5 Nature and contents of container

PVdC coated PVC/Aluminium blisters in pack sizes of 7, 10, 14, 20, 21, 28, 30, 50, 56 & 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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T/A Ivax Pharmaceuticals UK
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5-7 Broadhurst Gardens
Swiss Cottage
London, NW6 3RZ
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8 MARKETING AUTHORISATION NUMBER

PA 282/26/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 02 August 1983

Date of last Renewal: 02 August 2008

10 DATE OF REVISION OF THE TEXT

June 2010